Rapid Nucleophilic Substitutions on Cyclopentadienyl Iodide and Bromide

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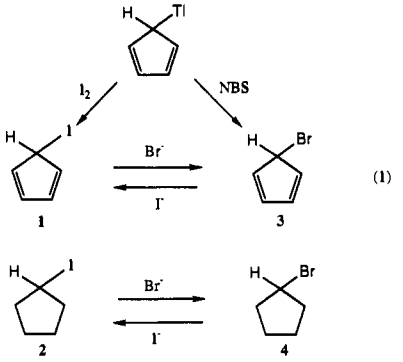
Abstract: Cyclopentadienyl iodide reacts with tetrabutylammonium bromide to afford cyclopentadienyl bromide ca. 10 times as rapidly as cyclopentyl iodide reacts under the same conditions. Cyclopentadienyl bromide reacts with tetrabutylammonium iodide ca. 10^3 times as rapidly as does cyclopentyl bromide. To check for allylic substitution, 5-iodocyclopentadiene was metallated with potassium hexamethyldisilazide, and the resulting anion was quenched with D_2O/CF_3CO_2D to afford 5-iodo-5-deuteriocyclopentadiene. This could be trapped when kept very cold, but on warming to room temperature it underwent iodine migration that rapidly scrambled the deuterium position. The high reactivity of the cyclopentadienyl halides in substitution under these conditions is in sharp contrast to their low reactivity under solvolytic S_N1 conditions. The possible mechanisms and reasons involved are discussed.

Some years ago we described the synthesis of 5-iodo-, 5-bromo-, and 5-chlorocyclopentadiene and various of their reactions.[1-3] The Ag^+ assisted solvolysis of the iodide **1** was at least 10^5 slower than was the same reaction with the cyclopentyl iodide **2**, reflecting the antiaromaticity of the cyclopentadienyl cation. Bromocyclopentadiene was used to generate and characterize this unstable cation.[4] We have now examined the reactivity of the cyclopentadienyl iodide **1** and the bromide **3** in the presence of nucleophiles. Again we have compared them with the corresponding saturated analogues **2** and **4**. The results are quite different from those seen under our previous solvolysis conditions.

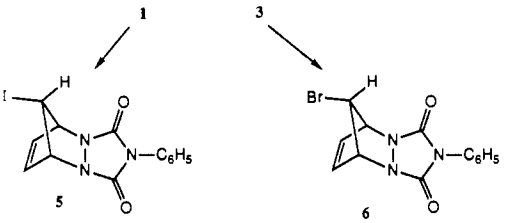
Most nucleophiles convert **1** and **3** to uncharacterizable products, probably because of the instability of simple 5-substituted cyclopentadienes such as **1** and **3** and their easy isomerizations. We were able to study the substitution on **1** by tetrabutylammonium bromide and the substitution on **3** by tetrabutylammonium iodide, to interconvert the two compounds (eq 1). In



(1)

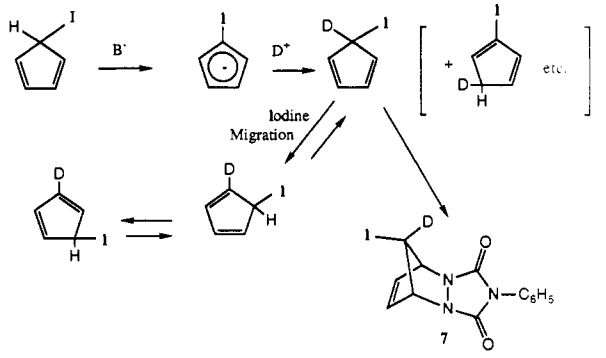
both cases we also saw nucleophile-induced proton migration to isomerize the substrates, so we determined initial rates of substitution in 1/1 (v/v) CCl_4–CH_3CN at 25.0 °C using GLC analysis for the starting material and product. The rate data are listed in Table I.

As the data show, the rate of conversion of **1** to **3** is first order in $Bu_4N^+Br^-$ over a 40-fold concentration range. The second-order rate constant is ca. 10 times as large as that for reaction of saturated **2**. Thus the two double bonds in **1** *increase* its reactivity. Similarly, cyclopentadienyl bromide (**3**) is faster than its saturated analogue **4** in reaction with $Bu_4N^+I^-$, in this case by ca. 10^3 fold.



The reaction of **3** was accompanied by very rapid competing isomerization; the rate constant reported is that of the initial rate for the appearance of product.

Nucleophilic substitution reactions are known on hexachlorocyclopentadiene and related compounds. It seems likely, and has been suggested, that they proceed by an S_N2' mechanism.[5] We attempted to look for such an allylic displacement mechanism in our case by deuterium labeling. A solution of **1** in 2:1 ether–benzene was converted to the anion of **1** with potassium hexamethyldisilazide at −15 °C and then cooled to −78 °C and quenched with D_2O–CF_3CO_2D. After 20 min the resulting **1** was trapped with *N*-phenyltriazolinedione (NPTD). [We have previously described[1,3] the adducts **5** and **6**, as well as the adduct of 5-chlorocyclopentadiene with NPTD.] The adduct was 40% d_1 (mass spectrum) with 40% of the deuterium at the (original) C-5 position as shown in **7** (NMR). If instead the deuterated **1** solution



was taken briefly to −15 °C before cooling again to −78 °C and trapping with NPTD, the NMR of the resulting adduct showed that the deuterium had been randomly distributed over all the cyclopentadiene positions.

This shows that the iodine atom of **1** rapidly moves around the ring under very mild conditions, and we have also seen this rapid movement of iodine in **1** at 22 °C (but not at −40 °C) by ^1H NMR magnetization transfer experiments. The iodine migration in **1** is related to other known 1,5 shifts of 5-substituents on the cyclopentadiene ring.[6,7] Our previous studies[3] showed that hydrogen

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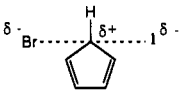
Table I Nucleophilic Substitution Reactions

substrate	nucleophile[f]	k, M^{-1} min^{-1}
1	0.01 M TBABr	0.20 ± 0.05[b]
1	0.1 M TBABr	0.16 ± 0.07[c]
1	0.2 M TBABr	0.27 ± 0.04[d]
1	0.2 M TBABr[e]	0.33[a]
1	0.3 M TBABr	0.22 ± 0.08[b]
1	0.4 M TBABr	0.23 ± 0.06[b]
2	0.1 M TBABr	0.019 ± 0.003[d]
3	0.1 M TBAI	0.4 ± 0.2[d]
3	0.1 M TBAI[e]	1.4 ± 0.7[a]
4	0.1 M TBAI	0.00033 ± 0.00002[c]

[a] One run. [b] Average of two runs. [c] Average of three runs. [d] Average of four runs. [e] Solution was 0.01 M in 2,6-di-*tert*-butylphenol. [f] TBABr, tetrabutylammonium bromide; TBAI, tetrabutylammonium iodide.

migration in **1** is much slower, and controls show that it is not being catalyzed in the present case. The rapid iodine migration in **1**-5*d*, faster than the substitution by Br^-, makes it impossible to use this labeling to examine whether our displacement reaction goes with allylic substitution. Unfortunately the bromocyclopentadiene **3** was destroyed when we tried to deuterium label it in this way; NMR studies show that unlike iodine the Br does not rapidly migrate at room temperature.

There are several possible explanations for the observed accelerations in substitution reactions of **1** and **3**. They certainly exclude an S_N2 mechanism that has cationic character on the carbon atom (cf. **8**), considering the demonstrated[1] high energetic instability of the cyclopentadienyl cation. Our cases might involve simple S_N2 displacement at C-5 of **1** or **3**, with stabilization because of cyclopentadienyl *anion* character in the transition state (cf. **9**). Anionic character on the carbon atom in S_N2 reactions



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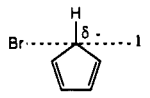

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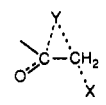

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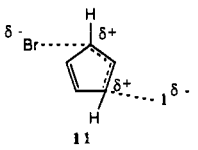

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is often invoked to explain the high reactivity of α-halo ketones and related systems,[8,9] although in those cases acceleration because the nucleophile σ bonds both to the substituting carbon and to the carbonyl carbon (cf. **10**) seems at least as likely[10] and fits the known data.

Another possibility is an S_N2' reaction, as discussed above. Even if its transition state had positive character, this should be largely localized to the allylic system involved (cf. **11**) and the transition state thus not destabilized. Cyclopentenyl bromide is even more reactive than is **3**. There are also various versions of electron-transfer mechanisms, either with discrete intermediate radicals[11,12] or as part of a transition state.[13-15] Radical *chain* reactions are excluded by our finding that the rates of our substitution reactions are unaffected by the presence of 2,6-di-*tert*-butylphenol. Our reactions might even involve displacement on the halogen atom to form a dihalogen molecule and cyclopentadienyl anion in a cage and then recombination. Reaction of **1** with $Bu_4N^+CN^-$ affords equal low yields of 5-cyanocyclopentadiene and of cyclopentadiene itself, both isolated as NPTD adducts; presumably the reduction product is formed by displacement on iodine. However, no such reduction of **1** is seen with $Bu_4N^+Br^-$, and this seems less likely than the other paths described.

No mechanistic information can be deduced from the fact that the reaction of **3** with I^- is ca. 100 times more accelerated than is the reaction of **1** with Br^-. Since they are run under essentially the same conditions (which are also used for the reactions of **2** and **4**), the principal of microscopic reversibility requires that the two displacements have the same transition state. The difference in rate accelerations must therefore reflect starting material energies, probably inductive destabilization of **3** relative to **1** by the greater electronegativity of bromine, taking **2** and **4** as standards. [The data in Table I also show that reaction of **4** with I^- is ca. 10^2 slower than the reaction of **2** with Br^-. In polar aprotic solvents bromide ion is a better nucleophile than iodide, and a poorer leaving group.[16]]

Although further work will be needed to elucidate the detailed mechanism involved, it is striking that the two sets of reaction conditions lead to such differences. Under S_N1 solvolytic conditions the cyclopentadienyl halides are completely unreactive, but with added alkylammonium halide salts they are significantly more reactive than are the cyclopentyl compounds.

Experimental Section

Materials. Iodobenzene was washed with sodium bisulfite and distilled. Carbon tetrachloride was filtered through alumina and distilled acetonitrile (Spectrograde, Aldrich) was passed through alumina immediately before use. Tetrabutylammonium salts were recrystallized several times from benzene/hexanes and dried in vacuo. Cyclopentyl iodide (Lancaster) was filtered through alumina and distilled. Cyclopentyl bromide (Aldrich) was passed through alumina immediately before use.

5-Iodocyclopentadiene (1).[1] Cyclopentadienyl thallium (0.30 g, 1.1 mmol) was slurried in 3 mL of dry CCl_4 (or benzene) and cooled in a CO_2–dioxane bath (12 °C). A solution of iodine (0.23 g, 0.91 mmol) in 10 mL of CCl_4 (or benzene) was added dropwise, allowing the purple color to completely disappear between drops (60 min total addition time). The mixture was filtered into a cooled filtration flask and stored at −78 °C under nitrogen. The resulting solution was approximately 10–20 mM in 5-iodocyclopentadiene when prepared in this way. ^1H NMR (400 MHz, 10% CCl_4–THF-d_8): δ 6.44–6.42 (m, 2 H), 6.37–6.35 (m, 2 H), 5.46 (heptet, J_{app} = 0.7 Hz, 1 H). GC/MS (DB-5 column, CI, CH_4, m/e): 193 (M + 1).

The Diels–Alder derivative[1] **5** was prepared by adding 1 equiv of *N*-phenyltriazolinedione (0.1 M solution in CH_3CN) to an aliquot of the solution described above. The addition was monitored by disappearance of the red color. ^1H NMR (200 MHz, $CDCl_3$): δ 7.49–7.33 (m, 5 H, ArH), 6.45 (ddd, $J_{5,6} = J_{6,8}$ = 1.8 Hz, $J_{6,10} < 1$ Hz, vinyl H), 5.14 (ddd, $J_{5,6} = J_{5,7}$ = 1.8 Hz, $J_{5,10}$ = 1.6 Hz, 2 H, bridgehead H), 4.38 (br s (tt), $J_{5,10}$ = 1.6 Hz, $J_{6,10} < 1$ Hz, ICH, 1 H), couplings determined by homonuclear decoupling experiments. MS (CI, NH_3): m/e 387 (M + NH_4^+ + 2, 1.4%), 386 (M + NH_4^+ + 1, 15%), 385 (M + NH_4^+, 100%), 368 (M + H^+, 20%).

5-Bromocyclopentadiene (3).[3,4] A slurry of cyclopentadienyl thallium (0.37 g, 1.4 mmol), freshly recrystallized *N*-bromosuccinimide (0.185 g, 1.04 mmol), and CCl_4 (6 mL) was stirred at 0 °C for 30–45 min. The solution was filtered into a cold (0 °C) suction flask and stored at −78 °C until needed. ^1H NMR (400 MHz, 10% CCl_4–THF-d_8): δ 6.42–6.40 (m, 2 H), 6.39–6.36 (m, 2 H), 5.01 (br s, 1 H).

The Diels–Alder adduct[2] **6** with *N*-phenyltriazolinedione was prepared as described above. ^1H NMR (200 MHz, $CDCl_3$): δ 7.5–7.3 (m, 5 H, ArH), 6.46 (ddd, $J_{5,6} = J_{6,8}$ = 1.8 Hz, $J_{6,10} < 1$ Hz, vinyl H), 5.14 (ddd, $J_{5,6} = J_{5,7} = J_{5,10}$ = 1.8 Hz, 2 H, bridgehead H), 4.40 (br s (tt), $J_{5,10}$ = 1.8 Hz, $J_{6,10} < 1$ Hz, BrCH), couplings determined by homonuclear decoupling experiments.

5-Deuterio-5-iodocyclopentadiene (1-5*d*). A solution of KN(Si-$(CH_3)_3)_2$ in toluene (1 mL, 0.5 M, Aldrich) was added to 1 mL of dry THF in a dry flask under nitrogen. The solution was cooled to −15 °C, and a 10 mM solution of iodocyclopentadiene (1 mL) was added dropwise over 5 min. The solution was stirred for 20 min at −15 °C and then

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cooled to −78 °C. A solution of 50% D_2O–CF_3CO_2D was added, and stirring was continued for 20 min. A 0.2 mM solution of *N*-phenyltriazolinedione in acetonitrile was added dropwise until the pink color persisted. The product **7** was isolated by extractive isolation (CH_2Cl_2–H_2O) and purified by preparative TLC (silica, $CHCl_3$). MS (CI, NH_3): *m/e* 387 ($M + NH_4^+ + 2$, 30%), 386 ($M + NH_4^+ + 1$, 100%), 385 ($M + NH_4^+$, 80%). ^1H NMR (200 MHz, $CDCl_3$): δ 7.5–7.3 (m, not integrated), 6.46 (m, integral = 35), 5.14 (m, integral = 32), 4.40 (br s, integral = 11).

Kinetics. A solution of iodobenzene at 5.0 or 0.50 mM (internal standard) with various concentrations (cf. Table I) of tetrabutylammonium halide in acetonitrile was prepared (solution A). Another solution (solution B) was prepared of 5.0–50 mM substrates **1–4** in CCl_4. Equal volumes of solutions A and B were combined, shaken, and incubated at 25.0 °C in a temperature bath. Aliquots (250 mL) were periodically removed and filtered through 0.4–0.6 g of silica in a Pasteur pipet, eluting with 1.2 mL of CCl_4. The eluant was frozen in dry ice until it could be analyzed by gas chromatography.

Gas chromatographic analysis was carried out with a Varian Model 3700 gas chromatograph equipped with a 30 m × 1.5 μm DB1 column and FID detector. The injector temperature was maintained at 200 °C (higher temperatures resulted in 1,5-proton migration in the cyclopentadienes). The aliquot was warmed to ambient temperature, and either 0.5 or 1.0 μL was injected, depending on the anticipated concentration of the species to be assayed. One of three temperature gradient programs was initiated: (a) 40 °C for 2 min, increase 30 deg/min until 200 °C (halocyclopentadienes); (b) 45 °C for 2 min, increase 30 deg/min until 200 °C (cyclopentyl iodide); (c) 70 °C for 3 min, increase 40 deg/min until 200 °C (cyclopentyl bromide). Every attempt was made to maintain consistency of injection size, temperature program, and peak integration technique within each run, and for the calibration curve for that run.

The ratios of the integrated peaks corresponding to appearing product and internal standard were determined. These data and the relative response factor for the product versus the internal standard were used to calculate the initial rate for each reaction in the standard way. Reactions were followed only until 5% of the starting alkyl halide had disappeared, so no logarithmic plot was required. At high nucleophile concentrations and especially with compound **3** the depletion of the starting cyclopentadienyl halide due to 1,5-proton migration was rapid, and the initial rate was extrapolated from a plot of the observed rate vs time.

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Modular Design of Synthetic Protein Mimics. Crystal Structure of Two Seven-Residue Helical Peptide Segments Linked by ε-Aminocaproic Acid

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Abstract: Two seven-residue helical segments, Val-Ala-Leu-Aib-Val-Ala-Leu, were linked synthetically with an ε-aminocaproic acid (Acp) linker with the intention of making a stable antiparallel helix–helix motif. The crystal structure of the linked peptide Boc-Val-Ala-Leu-Aib-Val-Ala-Leu-Acp-Val-Ala-Leu-Aib-Val-Ala-Leu-OMe (**1**) shows the two helices displaced laterally from each other by the linker, but the linker has not folded the molecule into a close-packed antiparallel conformation. Two strong intermolecular NH···O=C hydrogen bonds are formed between the top of the lower helix of one molecule and the bottom of the upper helix in a laterally adjacent molecule to give the appearance of an extended single helix. The composite peptide with Boc and OMe end groups, $C_{76}H_{137}N_{15}O_{18}\cdot H_2O$, crystallizes in space group $P2_1$ with a = 8.802 (1) Å, b = 20.409 (4) Å, c = 26.315 (3) Å, and β = 90.72 (1)°; overall agreement R = 7.86% for 5030 observed reflections ($|F_o| > 3\sigma(F)$); resolution = 0.93 Å. Limited evidence for a more compact conformation in solution consistent with an antiparallel helix arrangement is obtained by comparison of the HPLC retention times and CD spectra of peptide **1** with well-characterized continuous helices of similar length and sequence.

The design and construction of synthetic mimics for folding motifs in proteins has attracted considerable recent interest.[1] A modular approach illustrated in Figure 1 is being developed in these laboratories, which envisages stepwise assembly of conformationally rigid helices into super-secondary structures like the α,α motif by means of intervening flexible linker sequences.[2] This strategy relies on the ability of α-aminoisobutyric acid (Aib)[3] to stabilize helical structures in oligopeptides.[4] The systematic investigation of the effects of Aib content, precise positioning of Aib residues, chain length, and sequence have led to the synthesis and characterization in crystals of several helical oligopeptides.[5] These peptides have yielded predominantly α-helical conformations, ranging in length from 2 to 4 helical turns, and can serve, in principle, as the structurally defined modules in further assembly. In this paper we describe the joining of two helical segments by a flexible linker residue, ε-aminocaproic acid (Acp). The two end moieties of the linker, NH and $C^{\alpha}H_2C{=}O$, should provide hydrogen bonding groups that serve to continue the helical conformation of the individual modules, while the central $(CH_2)_5$

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(3) (a) Abbreviations used: Aib, α-aminoisobutyric acid; Acp, ε-aminocaproic acid; Boc, (*tert*-butyloxy)carbonyl. (b) For definitions of torsional angles, see: IUPAB-IUB Commission on Biochemical Nomenclature. *Biochemistry* **1970**, *9*, 3471–3479. (c) All chiral amino acids are of the L configuration.

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